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Therapy-Related Acute Myeloid Leukemia With t(8;21) in a Child With Previous Ewing's Sarcoma

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Cases of secondary acute myeloid leukemia (AML) occurring after treatment for an Ewing's sarcoma are uncommon. Therapy-related AML with t(8;21) translocation is an entity which has been well characterized. A case of AML-2 with t(8;21) and t(3;15) occurring 4 years after treatment for an Ewing's sarcoma with cyclophosphamide, doxorubicin, vincristine, dactinomycin, and radiotherapy, is reported. Autologous bone marrow transplantation was performed during second remission, 23 months after diagnosis. Reverse transcriptase polymerase chain reaction of the AML1/ETO fusion gene product was performed in order to monitor the quality of the remission. The patient currently remains in remission 24 months after the bone marrow transplantation. Med. Pediatr. Oncol. 29:132–134, 1997.

Key words: acute myeloid leukemia; Ewing's sarcoma; translocation t(8;21)(q22;q22); translocation t(3;15)(p22;q21); AML1/ETO mRNA

INTRODUCTION

Acute myelogenous leukemia (AML), developing after treatment with a variety of chemotherapy agents, particularly alkylating agents and epipodophyllotoxins, is a well-described entity [1]. Therapy-related acute myelogenous leukemia (t-AML) with t(8;21)(q22;q22) translocation has also been previously reported [2]. Nevertheless, it remains a rare event particularly in children [2]. Translocation t(3;15)(p22;q21) is not known in AML [3]. Here we describe a new pediatric case of t(8;21) and t(3;15) AML occurring 4 years after treatment for an Ewing's sarcoma. Detection of minimal residual disease (MRD) by reverse transcriptase polymerase chain reaction (RT-PCR) of AML specific translocation was performed. Prognostic value of AML1/ETO mRNA detection has been described [4]. In our case, availability of this information did not allow the monitoring of the hematological status of the patient after therapy.

Case Report

An 8-year-old boy was admitted to our institution in March 1988, for lameness of the right hip, tiredness, abdominal pain, nausea, as well and fever for 4 weeks. No particular previous history was mentioned. On admission, a swelling of the hip was palpable, and was confirmed by X-ray radiography. The computerized tomographic scanning found a 8 × 6 cm mass without node involvement. Histology revealed small indifferenciated round cells of an Ewing's sarcoma. Bone marrow aspiration showed a cluster of metastatic cells. Cytogenetics found a t(11;22) translocation (Table I). The patient was treated according to the protocol EW88 of the French Society of Pediatric Oncology including five courses of cyclophosphamide (150 mg/m^2, 7 consecutive days) and doxorubicin (35 mg/m^2, 8th day). The clinical course was eventless during neutropenia. Response to this first round of chemotherapy was good, with an almost total regression of the tumor burden 4 months later (July 1988). Pathologic examination of the resected specimen demonstrated >95% tumor necrosis. Surgical resection of the bone residual mass was followed by irradiation of the right hip (40 gray) and a maintenance chemotherapy (11 injections of vincristine 1.5 mg/m^2/week associated with five injections of dactinomycin 1.5 mg/m^2/2 weeks), then a second round of treatment (five injections of cyclophosphamide and doxorubicin followed by 11 injections of vincristine associated with five injections of dactinomycin with doses as mentioned above) performed between October 1988, and April 1989.

In May 1992 (4 years after the previous diagnosis), examination revealed a splenomegaly and a purpura. Laboratory findings were: Hb = 10.3 g/dl, white blood cells (WBC) = 41.5 × 10^9/l (with 80% blasts), platelets = 106 × 10^9/l. Bone marrow aspirates were hypercellular with 81% of blasts with Auer rods (AML-2). Cytogenetics found a clone with two translocations t(8;21)

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TABLE I. Cytogenetic and Molecular Data

Date	Stage	Karyotype number of metaphases	RT-PCR Couple of Primers[c] AML1C/ETO	RT-PCR Couple of Primers[c] MTG8/AML1C	RT-PCR Sensibility number of cells
March 1988	Ewing/diagnosis	46,XY,t(11;22)(q24;q12) [6]	ND	ND	
May 1992	AML[a]/diagnosis	46,XY,t(3;15)(p22;q21),t(8;21)(q22;q22) [20]	+	+	20,000,000
August 1992	AML/CR[a]	ND[a]	−	+	5,000,000
August 1993	AML/relapse	46,XY,t(3;15)(p22;q21),t(8;21)(q22;q22) [18]	ND	ND	
December 1993	AML/CR	46,XY [20]	−	+	2,000,000
February 1994	BM harvest (before purge)	ND	−	−	100,000
	BM[a,b] harvest (after purge)	ND	−	−	300,000
After BM transplant	CR	ND	ND	ND	

[a]AML, acute myelogenous leukemia; CR, complete remission; BM, bone marrow; ND, not done.
[b]All karyotypes were performed on BM cells.
[c]Primer sequence: AML1C, AGCCATGAAGAACCAGG; ETO, AGGCTGTAGGAGAATGG; MTG8, GCGAACTCTTTCTCCTATC; AML1C, GAGGGAAAAGCTTCACTCTG.

and t(3;15). RT-PCR with two different couple of primers [5,6] detected a rearrangement between the AML1 and ETO genes confirmed on two independent cDNAs.

Chemotherapy was started according to the protocol LAME 91 of the French Society of Pediatric Hematology and Immunology. Induction therapy consisted of mitoxantrone 12 mg/m^2/day, day 1 to day 5, and cytosine arabinoside 200 mg/m^2/day, day 1 to day 7. Complete remission was achieved in July 1992. Maintenance chemotherapy consisted of etoposide 100 mg/m^2/day, 4 days; daunorubicin 40 mg/m^2/day, 4 days; cytosine arabinoside 100 mg/m^2/day, 4 days. Postremission treatment was cytosine arabinoside 25 mg/m^2/day, 4 days each month, 6-mercaptopurine 50 mg/m^2/day continuously for 7 weeks. During the postremission treatment, AML1/ETO RT-PCR detection remained positive with one assay. In August 1993, 10 days after the end of the treatment, examination found a hepatomegaly and diffuse ecchymotic lesions. Laboratory findings revealed Hb = 9.8 g/dl, WBC = 2.3×10^9/l (with 22% blasts), platelets = 57×10^9/l. Bone marrow aspiration was hypercellular with 34% of blasts with Auer rods, and 42% of dysplastic granulocytic lineage cells. Cytogenetics showed the same clonal anomalies as at the diagnosis. RT-PCR was not performed. Chemotherapy consisted of bisantrene 200 mg/m^2/day, 3 days; carboplatin 200 mg/m^2/day, 3 days; etoposide 100 mg/m^2/day, 3 days. After the first round, splenomegaly persisted and 6% of blasts were present in the bone marrow aspirate. Complete remission was achieved after the second round in October 1993 (same chemotherapy but 5 days). From October to December 1993, three cycles of chemotherapy were administrated with cytosine arabinoside, 25 mg/m^2/day, 3 days; bisanthrene 200 mg/m^2/day, 3 days. In December 1993, bone marrow aspirate showed complete remission. Cytogenetics was normal. RT-PCR was positive for t(8;21) AML1/ETO fusion transcript product with one assay, as mentioned in August 1992. Then the patient received five courses of cytosine arabinoside 5 days, concomitant with G CSF 5 μg/kg/day. In February 1994, RT-PCR was negative for both assays for the t(8;21) AML1/ETO fusion transcript product. Bone marrow was harvested and was purged in vitro with mafosfamide. Autologous bone marrow transplantation was performed in April 1994. Conditioning regimen was: busulfan 120 mg/m^2/day from day −10 to day −7, cyclophosphamide 50 mg/kg/day, and mesna 3,600 mg/m^2/day from day −6 to day −3.

Currently, the patient remains in complete remission 26 months after the second complete remission, and 24 months after the bone marrow transplantation. Anthracycline cumulative dose-related myocardial cell damage had lead to a decrease of the heart ejection fraction.

DISCUSSION

We reported a case of therapy-induced AML with t(8;21) in a child treated for an Ewing's sarcoma following administration of cyclophosphamide, doxorubicin, vincristine, dactinomycin and radiotherapy.

The clone was characterized by two balanced translocations t(3;15)(p22;q21) and t(8;21)(q22;q22). t(3;15) has not yet been described in AML-2 [3]. This abnormality is very uncommon in hematologic diseases and more likely found in solid tumors [3].

Secondary AMLs with t(8;21) are usually characterized by a short latent period, absence of preleukemic phase, a previous treatment combining a drug that targets topoisomerase II (etoposide or teniposide) generally associated with another drug (anthracycline, cyclophosphamide, cisplatin) and often with radiotherapy [2]. Secondary AMLs with t(8;21) are a disorder, occurring in about 3.4% of all the therapy-related AMLs [3].

A review of the literature [2] found 26 patients with therapy-related AML with t(8;21). Prior cancer was a solid tumor in 14 cases, and a haematologic malignancy in the other patients. Four out of 26 patients were under 17 years old. Three had lymphoma, one an osteosarcoma. According to our knowledge, our patient is the first case presenting a t(8;21) therapy-related AML after treatment of an Ewing's sarcoma. The case with an osteosarcoma [7] was a 16-year-old boy with a tumor of the femur. Treatment had consisted of 10 courses of high-dose methotrexate with citrovorum factor (MTX-CF 12.5 g/m^2 per course) and vincristine (2 mg), then cis-diamminedichloroplatinum II (CDP 150 mg/m^2 every 2 weeks). No radiotherapy had been delivered. Interval between onset of treatment of the primary tumor and diagnosis of AML-2 without preleukemic phase had been 51 months, and 28 months after treatment completion. Cytogenetic was 45, X, -Y, t(8;21)(q22;q22). Treatment was high-dose cytosine arabinoside, vincristine, prednisone. Complete remission duration was 22 months. At this time, the patient relapsed with a similar cytogenetic result. The reinduction was successful. A second relapse occurred 2 years later. Overall survival from onset of the treatment was 46 months.

Therapy-related AMLs following treatment with epipodophyllotoxins have been-well documented [1]. Characteristics are a shorter latent period as compared to t-AML following alkylating agents delivery, FAB subtype M4 or M5, association to chromosomal translocations involving band 11q23. The risk of developing t-AML using high cumulative doses of topoisomerase II inhibitors (ALL regimen) is high (5–12% cumulative risk) [1,8]. By contrast, germ cell patients treated with low doses of etoposide have low risk for developing t-AML [1]. Incidence of t-AML for patients treated for rhabomyosarcoma was estimated to 7.6 for those receiving cyclophosphamide, and 51.6 for those receiving cyclophosphamide and etoposide [8].

AML carrying translocation fully characterized at the molecular level can be monitored for MRD with PCR approaches [5,6]. The t(8;21) translocation and detection of the AML1/ETO fusion gene have been already performed [9,10]. As in our case, these studies have shown that persistent PCR positivity can occur in patients both after remission induction by chemotherapy and after BMT [11]. The absence of detectable transcripts appeared to correlate with good prognosis in some patients [4]. Nevertheless, the prognostic value of the AML1/ETO mRNA fusion transcript detection in prolonged complete remission remains to be assessed [12]. Discordance between our PCR results using two different couples of primers could be explained by a mutation occurring between the sites of fixation of the primers ETO and MTG8 or, more likely, by a difference of sensibility between the assays.

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